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## Advances in the management of hypotension in septic shock

BY CLAUDIO MARTIN, MD.

New therapies such as recombinant human activated protein C (rhAPC) are emerging for the treatment of severe sepsis and septic shock,<sup>1</sup> but fundamental aspects for management of these patients must still be applied. These include the appropriate identification of the underlying infection, adequate antibiotic therapy, and surgical drainage when needed. When septic shock exists, the hypotension has to be treated to minimize hypoperfusion and further tissue injury. This issue of *Critical Care Rounds* summarizes recently published studies that provide guidance in this area.

Septic shock is a form of distributive shock with a generalized decrease in vascular tone and an increase in vascular permeability. These abnormalities result in the need for administration of large volumes of fluid and the frequent use of vasopressors. The goals of therapy should be to support the blood pressure and oxygen delivery to tissues. Several studies<sup>2</sup> have shown that there is no obvious benefit to supranormal levels of resuscitation. Thus, normal blood pressure and clinical signs of good tissue perfusion are reasonable therapeutic goals since untreated shock is clearly deleterious.

### Fluids

The flux of fluid from the plasma to the interstitial space is governed by Starling's equation:

$$J_v = K_f[(P_{mv} - P_t) - r(OP_{mv} - OP_t)],$$

where  $J_v$  is the flux,  $K_f$  is the filtration coefficient for fluid,  $P_{mv}$  is the hydrostatic pressure in the microvasculature,  $P_t$  is the hydrostatic pressure in the tissue,  $r$  is the reflection coefficient for large molecules,  $OP_{mv}$  is the oncotic pressure in the microvasculature, and  $OP_t$  is the oncotic pressure in the tissue. Classic teaching suggests that this equation results in net flux at the arteriolar end of a capillary, but the lower  $P_{mv}$  at the venous end produces movement of fluid back into the vascular compartment. Excess fluid can also be removed from the interstitial space through the lymphatic system.

The interstitial space is composed of a gel that contains hyaluronic acid, water, ions, and protein. In fact, 50% of total body extracellular protein is in the interstitial space. The value of  $r$  varies between tissues, but can increase during inflammation. Thus, plasma proteins such as albumin will move into the interstitial space, but will also be removed through lymphatic flow. Experimental demonstration of increased vascular permeability is actually obtained by measuring lymphatic protein concentration.<sup>3-5</sup> The changes that occur during sepsis in the interstitial gel and subsequently on the forces governing fluid flux are not known. Concern that colloid infusion will increase tissue oncotic pressure and thus increase tissue edema has not been demonstrated. Conversely, short-term clinical studies have shown that albumin increases extracellular fluid volume more than its infused volume, and more than an equivalent infusion of saline. Albumin increased plasma volume relative to interstitial volume in a 1:1



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ratio, compared to 1:3 for saline. This observation suggests that fluid is recruited from the intracellular space.<sup>6</sup> Intracellular edema has been demonstrated in animal models of sepsis,<sup>7</sup> and the synthetic colloid pentastarch reduces the amount of this edema and morphologic injury.<sup>8</sup> However, the effect of this reduction on organ function is not known.

Controversy exists primarily regarding the best choice of fluid. Reviews prepared by the Cochrane group concluded that colloids in general,<sup>9,10</sup> and albumin specifically,<sup>11</sup> were not of any benefit compared to crystalloid solutions. In fact, they stated that albumin was actually associated with increased mortality.<sup>11</sup> However, these reviews were criticized on the basis that the studies selected for the meta-analysis were not adequately assessed for the methodological quality of the intervention. Indeed, in a more recent meta-analysis of the general use of albumin, the authors concluded that albumin was safe.<sup>12</sup> However, a provocative accompanying editorial challenged these authors conclusions.<sup>13</sup>

A third review in the Cochrane database asked whether there were differences between different colloid solutions.<sup>14</sup> The conclusion was that there were no differences in mortality, but the primary studies in this analysis were also small, thus lowering confidence in the conclusion (Table 1).

A recent multicentre, randomized, clinical study with 129 patients, compared a synthetic hetastarch to gelatin for the resuscitation of patients with severe sepsis or septic shock.<sup>15</sup> This study was randomized with concealment, but not blinded. The pentastarch group appeared to have a greater degree of renal dysfunction at baseline. Primary outcome was acute renal failure, defined as the need for dialysis or a twofold increase in creatinine. With this definition, patients treated with the hetastarch had a higher incidence of acute renal failure, 42%, compared to 23% in the gelatin group ( $P=0.028$ , OR 2.32 with 95% CI, 1.02-5.34). However, the number of patients requiring renal replacement therapy was not different, so the endpoints were largely met by an increase in creatinine. Mortality, length of stay, and the cumulative volume replacement were not different. Other studies have used hemodynamic parameters as the primary outcome. For example, a small, randomized study compared 10% pentastarch to 20% albumin in critically ill patients.<sup>16</sup> The pentastarch group had a greater increase in calculated oxygen delivery compared to albumin. These studies suggest that differences may exist between colloids, but the significance of the surrogate outcomes is not known.

Currently, gelatin-based colloids are not available in North America. Hetastarch and albumin are the most commonly used colloid solutions in Canada. Dextrans are also available, but tend to be used for more limited indications that do not include volume expansion. Hetastarches are carbohydrate chains, characterized by their mean molecular weight and molar substitution ratio. The mean molecular weight reflects the fact that when hetastarches are manufactured, a wide range of sizes is produced.

	<b>Trials (patients)</b>	<b>RR (for mortality)</b>	<b>95% CI</b>
Albumin vs HES	20 (1029)	1.17	0.91 - 1.50
Albumin/PPF vs Gelatin	4 (542)	0.99	0.69 - 1.42
Gelatin vs HES	6 (597)	0.96	0.69 - 1.33

HES = hydroxyethylstarch  
PPF = plasma protein fraction

Purification can select for a narrower range of compounds, measured by the mean molecular weight. The molecular number is the most common size of a particular preparation. The molar substitution ratio is a measure of the amount of branching in the compound. Hetastarches are degraded intravascularly by circulating amylase. The kidneys in turn, clear the resultant fragments. A higher substitution ratio results in less rapid degradation and increases the half-life of the hetastarch. Pentastarch, available in Canada, has a mean molecular weight of 260 and a molar substitution ratio of 0.4 – 0.45. The product used in the study by Schortgen et al<sup>15</sup> had an average MW of 200 and a substitution ratio between 0.6 and 0.66. It is not known if these differences in composition are sufficient to result in different clinical effects. The carrier solution for pentastarch is normal saline. Theoretically, a hetastarch with an appropriate size and substitution ratio should exert an oncotic effect when infused, then be cleared by degradation, leaving only the effect of the carrier solution. A 500 ml infusion of such a hetastarch would produce a plasma expansion equivalent to about 2000 ml of saline. However, saline will expand the extravascular space by around 1500 ml, while the saline component of the hetastarch solution would increase the extravascular space by about 365 ml (2/3 of 500 ml).

At present, we can only conclude that more research is needed to determine the optimal colloid solution, then to compare this solution to crystalloid.

### **Catecholamines**

Once plasma volume has been adequately restored, the ongoing presence of shock requires the use of vasoactive medications. Since sepsis usually manifests as hyperdynamic shock with a high cardiac output, vasoconstrictors are typically used to support blood pressure. However, relative ventricular dysfunction has been demonstrated in septic shock despite an apparently high cardiac output. Additionally, in the presence of pre-existing cardiac disease or with more severe cases of sepsis, cardiac output may be significantly depressed and require additional support.

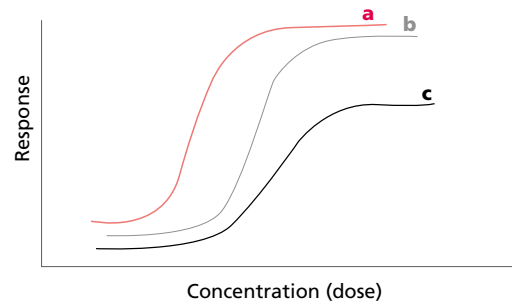
Evidence to support one catecholamine or combination over other choices in patients with septic shock is limited. One randomized, double-blind, single-centre study compared dopamine to norepinephrine in patients with septic shock.<sup>17</sup> The study duration was only a few hours and the outcome was the hemodynamic response, achieved

in a greater portion of patients with norepinephrine compared to dopamine. Dopamine and norepinephrine in patients with hyperdynamic sepsis were compared in another small, single-centre, randomized trial.<sup>18</sup> This study was also of short duration and found that whole body oxygen consumption increased with both agents. However, gastric intramucosal pH decreased slightly with dopamine, but increased with norepinephrine, suggesting that the latter is better for gut perfusion. A randomized, crossover trial in 10 patients with sepsis compared dopamine to dobutamine infused at a fixed dose of 5 µg/kg/min for 60 minutes each.<sup>19</sup> Both agents produced similar increases in systemic oxygen delivery, but different effects on measures of gastric perfusion. Dobutamine increased mucosal blood flow and decreased measures of mucosal acidosis (intramucosal pH, intramucosal pCO<sub>2</sub>, and pCO<sub>2</sub> gap), while dopamine decreased blood flow without any effect on mucosal acidosis. Obviously, the major limitations of all these studies are the short duration and the use of physiological outcomes that have not been validated as useful surrogate measures.

One study examined the effect of norepinephrine on mortality in a non-randomized cohort of 97 patients with septic shock.<sup>20</sup> With multivariate analysis, the use of norepinephrine reduced 28-day mortality to 55% compared to 82% in patients who did not receive norepinephrine ( $P < 0.001$ ). These rates seem high, but these data suggest that the patients had severe sepsis with shock. The study was not randomized, but two recent evaluations suggest that observational data can produce estimates of treatment effect similar to those from randomized, controlled trials.<sup>21,22</sup> Quality criteria for observational studies include: the use of well-specified inclusion and exclusion criteria; a defined entry time into the study; adjustment for baseline differences; and similarity in management apart from the intervention of interest.<sup>21</sup> In the norepinephrine study, patients were entered if they met criteria for refractory septic shock following admission to the ICU, although data on the interval between admission and study entry is not reported. Details are provided regarding antibiotic and hemodynamic therapy that show both groups were treated equally, except that the group receiving norepinephrine received lower quantities of dopamine. Despite the absence of randomization, important baseline factors appear remarkably well-balanced between the two groups, and the analysis was adjusted for risk factors that were identified by a preliminary univariate analysis.

Dopamine is often used at so-called “renal” doses with the belief that renal function will be protected or improved. A recent, multicentre, randomized, double-blind study compared low-dose dopamine to placebo in critically ill patients who had early signs of renal dysfunction.<sup>23</sup> There were 328 patients in 23 ICUs enrolled, with a variety of diagnosis. The presence of SIRS (systemic inflammatory response syndrome) was required for inclusion, but the prevalence of sepsis in the study was not reported. The infusion was continued until the patient

**Figure 1: Theoretical dose-response curves**



received renal replacement therapy, died, developed a serious adverse event related to the infusion, or had resolution of SIRS and renal dysfunction for at least 24 hours. The primary endpoint was the peak creatinine concentration at any time during the study. There was no difference between the two groups in the primary endpoint or in any of the secondary endpoints (increase in creatinine, creatinine clearance, creatinine > 300 µmol/L, renal replacement therapy, urine output).

In the absence of clear evidence, basic physiologic principles can provide some guidance. Alpha-adrenergic agonists produce vasoconstriction, while beta-adrenergic agonists cause vasodilation and increase cardiac contractility. Dopaminergic agonists on vascular smooth muscle exist preferentially in the splanchnic and renal circulations where stimulation results in vasodilation.<sup>24,25</sup> Dopamine has activity at each receptor, but with different sensitivities, as shown by the theoretical dose-response relations depicted in Figure 1. Thus, the dopamine receptor is activated at the lowest concentration (curve a), followed by beta-adrenergic receptors (curve b) and subsequently by alpha-adrenergic receptors (curve c). However, sepsis is known to decrease the sensitivity to adrenergic stimulation, which causes a right-shift in the dose-response curve (curves a, b, and c in Figure 1). The relative potency of dopamine at each receptor is most likely affected to varying extents, so it is difficult to know what effect is occurring at different doses. It appears more rational to use an agent such as noradrenaline or phenylephrine when vasoconstriction is required, and to add a beta-agonist such as dobutamine if the cardiac output needs augmentation. While weak, the evidence cited above appears to support this approach. Concerns that alpha-agents will worsen tissue ischemia do not appear to be valid, since the determinants of tissue perfusion are flow and pressure. These agents can be individually titrated to achieve the desired effect on systemic parameters. Whether management strategies that use measurement of regional perfusion (eg, gastric tonometry) can produce better clinical results requires further evaluation.<sup>26,27</sup>

### Vasopressin

The use of vasopressin for treatment of shock has recently become more commonplace. A small (10 patient),

randomized, placebo-controlled trial examined vasopressin infused at a fixed dose of 0.04 U/min for 24 hours.<sup>28</sup> Vasopressin resulted in improved hemodynamics and discontinuation of other pressors. Another randomized, placebo-controlled trial showed similar results during a short, 4-hour infusion, but presently is available only as an abstract.<sup>29</sup> In another report, a series of 16 patients with refractory septic shock were treated for 16 hours with vasopressin at 0.04 U/min.<sup>30</sup> Blood pressure and urine output improved, but decreased when the infusion was stopped. No adverse effects were noted. The authors make the hypothesis that vasopressin levels in septic shock may be abnormally low compared to other forms of shock because extremely high plasma levels are required to elicit a pressor response. Another recent case series included 35 patients with refractory septic shock who were treated with vasopressin.<sup>31</sup> Improvements in blood pressure and a reduction in norepinephrine requirements were noted, but liver enzymes and bilirubin increased while platelets decreased.

In summary, vasopressin seems to be an effective vasopressor in refractory septic shock. Most reports used a fixed dose of 0.04 U/min that produces a plasma level seen in other forms of shock. These data however, are mostly observational and use physiological endpoints. A multicentre, randomized, controlled trial has been initiated recently with funding from CIHR and sanctioned by the Canadian Critical Care Trials Group to test whether this treatment reduces mortality.

### Glucocorticoids

In the 1980's, 3 large, multicentre studies examined the use of high-dose methylprednisolone in

sepsis and ARDS.<sup>32-34</sup> Negative results and the possibility that this treatment actually increased the risk of infectious complications resulted in steroid therapy disappearing from use in patients with sepsis. More recent studies in ARDS<sup>35</sup> and sepsis<sup>36</sup> have resulted in a reevaluation of this therapy.

It has long been recognized and more recently confirmed, that the hypothalamic-pituitary-adrenal axis is impaired in sepsis.<sup>37,38</sup> In a multivariate model, the baseline cortisol level and the increase in response to stimulation with corticotropin were found to identify 3 groups of prognoses.<sup>37</sup> The group with a low baseline cortisol together with a good response to corticotropin had a 28-day mortality of 26%. The group with either an elevated baseline or a poor corticotropin response had a 28-day mortality of 67%. The worst prognosis was for the group with an elevated baseline and a poor response (82%).

Several studies have demonstrated that therapy with glucocorticoids can decrease mortality or reduce vasopressor requirements in patients with septic shock (Table 2). One double-blind, placebo-controlled, randomized trial was stopped early because an interim analysis showed significance in the primary outcome: reversal of septic shock at day 7.<sup>39</sup> Patients with septic shock were eligible for the study after 48 hours of vasopressor therapy. Forty-one patients were analyzed and the numbers needed to treat were 2 for shock reversal and 3 for mortality! Another randomized study of 40 patients did not find the same results, but did find that shock and organ dysfunction resolved more rapidly with steroid therapy.<sup>40</sup> Finally, a large, multicentre study from France, only presented in abstract form, also found a mortality benefit with steroid therapy.<sup>41</sup> In this study, hydrocortisone was

Study	Population	Intervention	Outcome (1) primary (2) secondary	Rate (Intervention/ Control)	ARR (95% CI)
Bollaert <sup>39</sup> n=41	Septic shock, vasopressor > 48h	Hydrocortisone 100 mg I.V. q8h for 5 days or longer; taper over 6 days	(1) Shock reversal	68% vs 21%	47 (17, 77)
			(2) 28 d mortality	32% vs 63%	31 (1, 61)
Briegel <sup>40</sup> n=40	Septic shock, high cardiac output, vasopressor support	Hydrocortisone, 100 mg bolus, followed by 0.18 mg/kg/h until shock reversal, then 0.08 mg/kg/h for 6 d	(1) Shock reversal	18/20 vs 16/20	
			(2) Time course	Median time of vasopressor support = 2 days hydrocortisone vs 7 days placebo (P=0.005)	
Annane <sup>41</sup> n=299	Septic shock < 8 h; 17 French ICUs	Hydrocortisone 50 mg I.V. q6h + fludrocortisone 50 mg po daily for 7 days	(1) 28 day survival	Abstract publication only; data not available	RR 0.712 (0.53, 0.965)

ARR = absolute risk reduction

**Table 3: Mechanisms of action for glucocorticoids**

- **Correct relative adrenocortical deficiency**
- **Activation of IKB- $\alpha$  which results in inhibition of NF $\kappa$ B**
  - Inhibition of iNOS
  - Reversal of adrenergic receptor desensitization
  - Decreased transcription proinflammatory cytokines

IKB- $\alpha$  = I $\kappa$ appaB- $\alpha$   
NF $\kappa$ B = Nuclear factor kappa B  
iNOS = Inducible nitric oxide synthase

given in combination with fludrocortisone. All three studies measured adrenal responsiveness with short corticotropin stimulation tests. Interestingly, the response to this test was not associated with the effect of the intervention on the primary outcome.

In view of the above findings, the mechanism by which steroid therapy at these doses confers benefit is not clear. Table 3 lists some possible mechanisms, based on our understanding of the actions of glucocorticoids and the inflammatory cascade. More studies are required to clarify this issue, and perhaps to tailor more specific drugs. However, it appears that patients with septic shock should receive glucocorticoids in a dose of 50 mg every 6–8 hours for 5–7 days. Based on pathophysiology, it is not clear what fludrocortisone adds to the effect, so we will eagerly await the full publication of the French study.

### Other therapies

In addition to pharmacologic interventions in septic shock, high-volume hemofiltration has also been studied.<sup>42</sup> Twenty patients with refractory septic shock were treated with 35 L of ultrafiltration over a 4-hour period, followed by more conventional volumes for at least 4 days. Patients who showed an acute response during the 4-hour period (11 of 20) had higher 28-day survival (9 of 11) than non-responders (0 of 9). These results are certainly dramatic, but require further validation because these patients may not have received the interventions discussed above, or rhAPC, all of which are now known to be of benefit.

### Conclusion

This is an exciting time for critical care and treatment of sepsis. After decades of frustrating searches for optimal management strategies, we are now presented with several interventions that have been demonstrated to save lives. Fundamental support of the ABCs (Airway, Breathing, Circulation) should include volume-limited ventilation for patients with ARDS complicating the sepsis, and the use of appropriate fluids for volume resuscitation. Vasopressor

support should most likely be based on noradrenaline and dobutamine, although further studies are needed in this area. We await the results of ongoing studies to see if vasopressin has a role. Patients with septic shock should receive glucocorticoid therapy as described above, probably within a few hours of the diagnosis of septic shock. With the ABCs properly managed, attention can focus on specific therapy with antibiotics and novel drugs such as rhAPC. The challenge is to ensure that these strategies are appropriately implemented and to monitor the effectiveness in the general critical care population.

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